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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/701,265

Filing Date: November 04, 2003

Appellant(s): BAKER ET AL.

John A. Harrelson, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 04/30/2012 appealing from the Office action mailed 04/12/2011.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

10/701264, 10/701236, 11/054848, 10/701007, and 10/860265.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application: 120, 121, 124, 127, and 136-138.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Wyatt, et al. "Deoxynucleotide-containing Oligoribonucleotide Duplexes: Stability and Susceptibility to RNase V1 and RNase H" Nucleic Acids Research, v.17, no. 19 (1989), pp.7833-42.

Manche, et al. "Interactions Between Double-Stranded RNA Regulators and the Protein Kinase DAI" Molecular and Cellular Biology, v.12, No. 11 (November 1992), pp.5238-48.

Monia, et al. "Evaluation of 2'_modified Oligonucleotides Containing 2'-Deoxy Gaps as

Antisense Inhibitors of Gene Expression" The Journal of Biological Chemistry, v.268, No. 19 (July 5, 1993), pp.14514-22.

Shibahara, et al., European Patent Application, EP 0 339 842, published November 02, 1989.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 120, 121, 124, 127, and 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Wyatt et al.** (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), **Manche et al.** (Molecular and Cellular Biology 1992), **Monia, et al.** (1993, J. Bio. Chem., v.268:14514-22), and **Shibahara, et al.** (European Patent Application 0339842, published on 11/02/1989).

At the time the invention was made, those in the art routinely synthesized short duplexes containing ribonucleotide residues for the purpose of studying the activity and structural requirements of enzymes that bind or cleave nucleic acids. This is demonstrated by the teachings of Wyatt, et al., Manche, et al., and Monia, et al.

Wyatt et al. teach that sensitivity of DNA and RNA to nucleases depends upon both chemical and conformational differences. For example, the 2'-OH makes ribonucleotides susceptible to alkaline hydrolysis and cleavage by ribonucleases, a mechanism not available for cleavage of deoxynucleotides. Wyatt et al. further teach that RNase V1 is a widely used probe for double-stranded RNA that does not have a specific requirement for 2'-OH and is thus postulated to be like RNase H, which cleaves RNA-DNA duplexes. To probe the structural requirements of RNase V1 and RNase H, Wyatt et al. synthesized a series of 14-nucleotide duplexes wherein 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy- and ribo-nucleotides. These duplexes contain a sequence complementary to the ADCK2 gene (pages 7837-9).

Manche et al. teach that the protein kinase DAI, the double-stranded RNA- activated inhibitor of translation, is a pivotal cellular regulatory enzyme that is an important element in the host antiviral response. Despite its importance as a regulatory enzyme, the interactions between DAI and its RNA effectors were complicated and incompletely understood. To better understand these interactions Manche et al. analyzed interaction of the enzyme with RNA duplex molecules of specified sizes ranging from 15-104 nt (see figure 1) to study binding and protection of dsRNA as well as activation and inhibition of the kinase.

Monia, et al. used a duplex to study the ability of a first oligonucleotide to direct RNase H cleavage *in vitro* and for antisense activity against Ha-ras (p.14516, 4th paragraph; Figure 1; p.14518, Figure 4; p.14520, Figure 6). The duplex comprises first and second chemically synthesized 17-25-nucleotide long oligonucleotides wherein the first oligonucleotide is 100% complementary to the second oligonucleotide and to a target mRNA and the two

oligonucleotides are not covalently linked to each other (page 14516, 4th and 5th paragraphs and Figure 1). The first oligonucleotide is a 17-mer gapmer having phosphorothioate linkages, at least 4 deoxyribonucleosides (DNA) in the gap, and each wing comprising 2'-OMe-modified nucleotides. The second oligonucleotide is a 25-mer synthetic oligoribonucleotide (RNA) that is a portion of Ha-ras mRNA. The first oligonucleotide has 100% complementarity to Ha-ras and to the second oligonucleotide.

While Wyatt, et al., Manche, et al., and Monia, et al. demonstrate that production of short RNA-containing duplexes was routine in the art for the purpose of studying enzymes that bind or cleave nucleic acids, these references do not explicitly teach duplexes wherein a first oligonucleotide is an RNA gapmer and the references do not explicitly teach duplexes wherein both strands of the duplex are RNA gapmers.

Shibahara, et al. teach antisense oligoribonucleotides (RNA) for target mRNA (HIV) inhibition wherein the oligoribonucleotides comprise 2'-OMe-modified nucleotides (claim 1; pages 13-14). At page 4, Shibahara, et al. teach antisense oligonucleotides comprising phosphorothioate linkages and both ribonucleotides (RNA) and 2'-OMe-modified nucleotides, wherein the positions of RNA and the 2'-OMe-modified nucleotides are not specified and can be at any position within the oligonucleotide (see page 4, General Formula I and the definitions of X, X₁, Y₁, Q, and Q₁). At page 13, Shibahara, et al. indicate that the invention is an improvement over DNA antisense oligonucleotides in that 2'-O-methylribonucleotides are resistant to various nucleases, including RNase H and DNases, and they form duplexes with complementary RNAs that are more stable than DNA-RNA duplexes (last paragraph on page 13 to top of page 14). Shibahara, et al. also indicate that 2'-O-methylribonucleotides are less

expensive to prepare than are deoxyoligonucleotides (end of the paragraph spanning pages 13 and 14). Shibahara, et al. indicate that while the compounds of their invention show potent anti-AIDS activity, the mechanism of the activity has not been experimentally proven (page 15, lines 15 and 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make synthetic ribonuclease substrates wherein the substrate is an artificial duplex of a target RNA and a 2'-OMe-nucleotide-containing oligonucleotide because it was well known by those of skill in the art to study enzymes with such artificial substrates. It would have been obvious to use an artificial duplex of a target RNA and a 2'-OMe-nucleotide/RNA gapmer because Shibahara, et al. teach that 2'-OMe-nucleotide/RNA oligonucleotides are an improvement over DNA antisense oligonucleotides and because Monia, et al. teach antisense oligonucleotides having 2'-OMe-nucleotide/DNA oligonucleotides. One of skill could substitute RNA for DNA in the gapmer of Monia, et al. and would be motivated to do so to study the mechanism of action of the 2'-OMe-nucleotide/RNA antisense oligonucleotide of Shibahara, et al., such as by testing the duplexes as substrates for various dsRNases, while protecting the oligonucleotide from exonucleases. One of skill in the art would further be motivated to modify the target RNA strand of the duplex with 2'-OMe-modified nucleotides to prevent unintended nuclease degradation of the target strand during such studies. One of skill would be motivated specifically to modify the ends of the target and antisense oligonucleotides, such as in a gapmer pattern with two 2'-OMe-modified nucleotides at the 3'- and 5'-ends, so as to increase the stability of the oligonucleotides by protecting the oligonucleotides from exonucleases. One of skill would also recognize that maintaining an unmodified RNA gap in the target strand would

best simulate the *in vivo* condition of the target. Therefore, the claims would have been *prima facie* obvious to one of skill in the art at the time the instant invention was made.

(10) Response to Argument

Appellant argues, starting at page 5 of the 04/30/2012 Appeal Brief, that the applied references considered individually or together do not suggest the claimed subject matter as a whole. Specifically, Appellant argues that those of ordinary skill in the art would not have had any reason to design and produce the claimed oligonucleotides before applicants' invention in view of the description provided in the cited references and the state of the art at that time. Appellant also argues that those of ordinary skill in the art would not have had a reason at the time of the invention to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification, in view of the description provided in the cited references.

First, Appellant specifically addresses the teachings of the Wyatt article (Wyatt). Appellant first summarizes the teachings of Wyatt (see pages 5-6 of the Appeal Brief). Appellant concludes that Wyatt provides no teaching or suggestion to produce oligonucleotide duplexes wherein one strand is gapmer and the other strand has at least one 2'-sugar modification and, further, that Wyatt does not provide a reason to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex (page 6 of Appeal Brief). Appellant appears to interpret the rejection as being based primarily on the Wyatt reference because Appellant proceeds, stating that "the remaining references fail to supply the missing teaching or suggestion,

and thus fail to compensate for the deficiencies of the Wyatt article." This is not persuasive. As indicated in the rejection, Wyatt is relied upon, among other references, to demonstrate the state of the art at the time of the instant invention. Wyatt, like others at the time, made small RNA duplexes and incorporated 2'-H modifications into both strands to study RNase activity. Likewise, Manche, et al. and Monia, et al. also made oligonucleotide duplexes for studying nucleic-acid-dependent enzymes.

Appellant next addresses the Manche article (Manche). Appellant argues, in sum, that Manche would not have prompted one of ordinary skill in the art to introduce 2'-sugar modifications into both strands of an oligonucleotide duplex. Appellant bases this on the fact that Manche describes experiments for deciphering the activation of an RNA-binding protein, DAI, and that the artificial substrates used in the experiments were not chemically modified. This is not persuasive. Again, Manche is representative of the art at the time of filing, which was replete with examples of short nucleic acid duplexes useful for studying nucleic-acid-dependent enzymes. Appellant's reference to the declaration of Dr. Corey is addressed hereinafter.

At the bottom of page 6 of the Appeal Brief, Appellant addresses the Monia article (Monia). Appellant argues that Monia does not provide a teaching or suggestion to make chemically modified RNA duplexes having at least one sugar-modified nucleoside in both strands. Appellant summarizes the teachings of Monia at pages 6 and 7 of the Appeal Brief. Appellant then specifically argues that the Monia article contains nothing that would have prompted those of ordinary skill in the art to incorporate at least one modified sugar into both strands of an oligomeric compound duplex because 1) Monia teaches *in vitro* RNase experiments for which there would have been no reason to utilize substrates having chemical modifications in

both strands, and 2) Monia's experiments involving introduction of single-stranded gapmers into HeLa cells contained no design or objective to prompt one of ordinary skill in the art to incorporate chemical modifications into both strands of an oligonucleotide duplex, as presently claimed. This is not persuasive. As indicated in the rejection of record, Monia is representative of the art at the time of filing, which was replete with examples of short nucleic acid duplexes useful for studying nucleic-acid-dependent enzymes. Monia also teaches antisense oligonucleotides for inhibiting target gene expression wherein the oligonucleotides are modified in a gapmer motif. As indicated, these teachings contribute to the whole of the rejection.

In the paragraph spanning pages 7 and 8 of the Appeal Brief, Appellant summarizes the teachings of Shibahara and concludes that although Shibahara describes 2'-OCH₃ modification to antisense oligoribonucleotides, Shibahara does not describe or suggest any reason to introduce chemical modifications into oligonucleotide duplexes. This is not persuasive. Shibahara teaches RNA-based antisense oligonucleotides for HIV RNA target inhibition and that such antisense oligonucleotides are an improvement over DNA-based antisense oligonucleotides that operate via RNase H activation. Shibahara also indicates that the mechanism by which the RNA-based antisense oligonucleotides operate is not known. Thus, Shibahara invites those of skill in the art to conduct *in vitro* experiments, such as those being conducted at the time as reported by the cited references, to determine the mode of action of the anti-HIV antisense oligoribonucleotides. In so doing, one of skill in the art would have an interest in maintaining the integrity of the target RNA in the absence of the antisense oligonucleotide. Accordingly, one of ordinary skill in the art would readily recognize that simple modification to the target RNA would help to maintain target integrity. Appellant traverses this position.

Appellant argues that "those of ordinary skill in the art would not have had a reason to incorporate chemical modifications, such as 2'-sugar modifications, into both strands of oligonucleotide duplexes used as dsRNase substrates at the time of the invention because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred." In particular, Appellant emphasizes that 1) in the *in vitro* experiments described in the references, undesired nucleases were not present and that 2) in the experiments in which nucleic acids were introduced into cells or cellular extracts, only single-stranded oligonucleotides targeted against full-length RNAs were used and double-stranded duplexes were not utilized. Appellant concludes that the cited references fail to provide any reason to modify both strands of such duplexes. See pages 8-9 of the Appeal Brief. These arguments are not persuasive. Shibahara indicates that 2'-OCH₃-modified antisense RNA oligonucleotides are effective against HIV RNA and that the mechanism of action of such oligonucleotides is not known. Accordingly, in investigating the mechanism of action, one of skill in the art would be motivated to examine target degradation under cellular conditions. The target RNA of Shibahara is HIV RNA. Because of the biological danger of such a target and because the fate of the HIV target RNA is not known, the skilled artisan would be motivated to use a tractable and controllable artificial HIV RNA substrate, such as a labeled region of the HIV RNA that is targeted by the antisense oligoribonucleotide. In order to study the effects of the antisense oligoribonucleotide on the artificial target RNA, the skilled artisan would be required to use the artificial substrate and antisense oligoribonucleotide in a cellular extract. Those of skill in the art are well apprised of the pervasiveness of RNase enzymes in cellular extracts and, therefore, would know that the target RNA would require

protection from undesired nuclease activity, including exonuclease activity, and that such protection could be afforded by incorporating modifications in the target RNA as instantly claimed, at the end(s) of the target RNA.

Appellant then contends that the Declaration of David Corey executed August 5, 2009, as it pertains to the instantly applied Manche article, has not adequately been weighed. Appellant also refers to Baracchini. However, Baracchini is not currently cited. Appellant points out that Dr. Corey contends that Manche teaches away from the present composition because Manche provides no reason to use a duplex of less than 33 base pairs, provides no reason to provide 100% complementarity, and provides no reason to make chemically modified oligonucleotides (see bottom of page 9 of Appeal Brief). This is not persuasive. Manche contributes to the obviousness of the claims as indicated in the rejection. As indicated, the cited references as a whole render the claims *prima facie* obvious. Manche is representative of the art at the time, including experiments for discerning nucleic-acid-dependent enzyme activity and substrate specificity.

At the top of page 10 of the Appeal Brief, Appellant refers to Dr. Corey's declaration regarding the "teaching away" provided by Manche and Baracchini. The instantly appealed rejection does not cite Baracchini. Appellant's arguments regarding Manche have been addressed.

At pages 10-11 of the Appeal Brief, Appellant finally argues that because the rejection under 35 USC § 103 does not identify a prior art duplex and explain how it would have been obvious to modify the duplex to arrive at the instantly claimed subject matter, the rejection falls. This is not persuasive. Appellant appears to disregard the rationale provided in the rejection.

Nucleic acid duplexes were known and were used for studying enzymes and for inhibiting gene expression. Shibahara clearly explains that antisense 2'-OCH₃-modified RNAs are effective against HIV RNA by an unknown mechanism. Given the interest in elucidating nucleic acid-dependent enzyme function at the time, one of ordinary skill would be motivated to determine the mechanism of action of the antisense 2'-OCH₃-modified RNAs of Shibahara. Shibahara claims antisense 2'-OCH₃-modified RNAs within the instantly claimed size range and Monia teaches the gapmer pattern of modification, which maintains an area, the gap, of natural enzyme substrate. Furthermore, Shibahara indicates that the antisense 2'-OCH₃-modified RNAs appear to function better than DNA-based antisense 2'-OCH₃-modified oligonucleotides, such that one of ordinary skill would be motivated to substitute RNA for DNA in the Monia gapmer. Appellant appears to be misinterpreting this rationale, arguing that the rejection of record merely indicates such a substitution as possible, but not suggested by the cited art (see page 11 of the Appeal Brief). To the contrary, Shibahara provides a motivation to the skilled artisan to use RNA in place of DNA. Therefore, Appellant's allegation that the rejection is based on impermissible hindsight is not persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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